Complications of HBV Therapy

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Alpha-interferons and nucleoside/tide agents are widely used as antiviral therapies for human HBV infection, but only a minority of the estimated 400 million persons infected with either HBeAg-positive or HBeAg-negative strains has ever been treated. Expanded use of established and emerging antiviral therapies for HBV infection is desirable because of the efficacy of treatments and potential to alter progression and reduce development of hepatocellular carcinoma (HCC). It is crucial to recognize that widespread use of these therapies will amplify the numbers of persons at risk for adverse events (AEs) or serious adverse events (SAEs). Since duration of treatment with alpha-interferons is ≤12 months, such risks are not prolonged. In contrast, realization that nucleoside/tide agents chronically suppress HBV DNA replication and that discontinuation often results in severe flares of disease has led to prolonged treatment, exceeding the durations used to determine safety and efficacy for regulatory approval.

To assess complications of monotherapy with an expanding number of agents, data on AEs and SAEs were collated from published literature, manufacturers' databases, the FDA approval documents, and the FDA Office of Drug Safety. The AEs and SAEs observed with alpha-interferon monotherapy (with or without pegylation) were similar in nature and severity to those reported during treatment of HCV infections. Risks of neutropenia, thrombocytopenia, and depression require careful monitoring and response. Among the FDA-approved nucleoside/tide analogues (Lamivudine=LVD; adefovir=ADV; and entecavir=ETC), AEs included headache, URI, pharyngitis, cough, fever, asthenia, abdominal pain, back pain, fatigue, nausea, flatulence, and diarrhea. Although the cumulative incidence of all AEs was high (70-90%), they were generally of mild to moderate severity. The incidence of SAEs was low (3-8%) and often considered unrelated to the drugs. Discontinuations due to AEs ranged from <1% to 4%. Increases of serum creatinine ≥0.5 mg/dL occurred with ADV in 3% of patients during 5 years of therapy. Off-label use of tenofovir (TDF) for HBV therapy has also been associated with azotemia, and both ADV and TDF are rarely associated with renal tubular or glomerular dysfunctions of unknown significance. It is unclear if mild effects of ADV or TDF on PO_4 balance may demineralize bone. LVD and TDF have FDA Black Box warnings for severe exacerbations of hepatitis B after discontinuation of therapy and for lactic acidosis and severe hepatomegaly with steatosis. The FDA Patient Information Sheet describes similar risks for ETC. Long-term treatment of HBV infection with LVD was unassociated with convincing evidence of increased mitochondrial toxicity (lactic acidosis, pancreatitis, myopathy, neuropathy, and acute fatty liver). Flares of ALT during LVD therapy were often associated with increasing HBV DNA levels (resistance) and persisted until discontinuation. In contrast, ALT flares with ETC therapy were associated with decreasing HBV DNA levels and often abated during continued therapy. ALT flares with ADV were less frequent than in the placebo group and unassociated with rising HBV DNA levels. Death while on therapy ranged from 0% to <1%. Flares of ALT after discontinuation of therapy were more frequent following treatment with LVD than with

ETC. High doses of ETC are associated with malignant neoplasms in rodents, and malignancies were observed in both the ETC and LVD treatment groups during registration trials (hepatocellular carcinoma, basal cell carcinoma, breast and prostate cancer). Safety data from clinical trials of emerging therapies, such as telbivudine (LdT), emtricitabine (FTC), clevudine (L-FMAU), and pradefovir, are limited. Overall, LVD, ADV, and ETC treatment of HBV-infected persons for extended periods appears to be generally safe, but careful monitoring is required. Discontinuation of therapy may result in severe, life-threatening exacerbations of hepatitis B. The long-term effects of ADV, TDF, and pradefovir on renal function remain undefined.